UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 09/937,100 | 09/20/2001 | Francis J Carr | MERCK 2309 | 4360 |

23599 7590 08/25/2004

MILLEN, WHITE, ZELANO & BRANIGAN, P.C.
2200 CLARENDON BLVD.
SUITE 1400
ARLINGTON, VA 22201

| EXAMINER | |
|---|---|
| WESSENDORF, TERESA D | |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1639 | |

DATE MAILED: 08/25/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/937,100 | CARR, FRANCIS J | |
| | Examiner | Art Unit | |
| | T. D. Wessendorf | 1639 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *18 June 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *16-74* is/are pending in the application.

4a) Of the above claim(s) *16-51* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *52-74* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

## DETAILED ACTION

### *Status of Claims*

Claims 16-74 are pending in the application.

Claims 16-51 are withdrawn from consideration, as stated above.

Claims 1-15 have been cancelled.

Claims 52-74 are under examination.

### *Specification*

In view of the new abstract of the disclosure the objection no longer applies.

### *Response to Arguments*

Applicant states that an editable document was not readily available to Applicant, therefore, a substitute specification with appropriate line spacing has not been provided at this time. Applicant therefore requested that the examiner hold this rejection in abeyance.

Applicant states that a revised sequence listing will be provided in due course to reflect the sequences on pages 3, 5, and 26.

In reply, in the absence of a substitute specification and new sequence listing, the objection to the specification has not been overcome.

***Claim Rejections - 35 USC § 101***

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 52-63 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific asserted utility or a well established utility for reasons advanced in the last Office action.

***Response to Arguments***

Applicant urges that the invention provides new methods for isolating specific proteins from a complex mixture of such proteins by virtue of binding to a specific target. In particular, the invention provides methods for isolating specific antibody domains from a gene library derived mixture of such domains by virtue of binding to a specific target antigen. For the analysis of proteins, the invention provides new methods for analyzing complex mixtures of proteins. (Specification, page 1, lines 9-14). The claimed library recites specific structural features, which enable these methods to be carried out. In this respect, the library is no different than any other material, which is used in molecular biology and protein chemistry. For example, chromatography materials and fluorophores are utilized in methods of purifying and labeling proteins and DNAS of

interest. These uses are substantial and not excluded by any of the uses described on Pages 6-7 of the Revised Interim Utility Guidelines Training Materials. Moreover, the Patent Office routinely issues claims covering these categories of materials.

In response, applicant recites what is in the disclosure without specifically specifying just what exactly is the specific or substantial utility for the claimed library. The claims or the specification does not recite for any specific structure of the library. Analogy to the chromatographic materials is improper. These materials relate to a single and very specific compound component. However, the instant library is not specific and comprises collection of millions of compound. It is the individual compound in this collection that is known to possess a specific and substantial utility, not the library per se.

The court in *Brenner v. Manson*, 148 U.S.P.Q. 689 (1966), expressed the opinion that all chemical compounds are "useful" to the chemical arts when this term is given its broadest interpretation. However, the court held that this broad interpretation was not the intended definition of "useful" as it appears in 35 U.S.C. §101, which requires that an invention must have either an immediately apparent or fully disclosed "real world" utility. The court held that:

> The basic quid pro quo contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility. . . . [u]nless and until a process is refined and developed to this point-where specific benefit exists in currently

> available form-there is insufficient justification for permitting an applicant to engross what may prove to be a broad field. . . . a patent is not a hunting license. . . .[i]t is not a reward for the search, but compensation for its successful conclusion.

Until some actual and specific significance can be attributed to the library, one of ordinary skill in the art would be required to perform additional experimentation in order to determine how to use the claimed library. Thus, there was no immediately apparent or "real world" utility as of the filing date.

Claims 52-63 is also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

***Claim Rejections - 35 USC § 112, first paragraph***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 52-74 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

A). The as-filed specification does not provide support for the newly added claims. For example, the as-filed specification does not support and describe "……a library wherein each of the proteins contain one or more individual identifier sequence amino acid **tracts** which are **unique** to said individual protein when bound to the specific target of interest……" (Underlinings supplied.) MPEP 714.02 clearly states that applicant should specifically point out where in the specification support for the newly added claims can be found. (See also claims 52-55 and 64-74.)

B). The specification fails to provide an adequate written description for the claimed library that cover a huge genus of a protein having no defined amino acid sequences. The undefined protein components do not recite amino acid sequences with an individual identifier sequence amino acid tracts. Nor does it describe how it

is unique and/or its position in the protein sequences. It does not describe whether it is the whole protein or the fragment that are flanked by the protease sensitive sites. Nor does it describe which sites are considered sensitive to a protease. There is no description as to the kind, type of protease and/or the kind of protein in the library to which said protease can be attached. A "written description of an invention involving a chemical genus, like a description of a chemical species, requires a precise definition, such as by structure, formula [or] chemical name of the claimed subject matter sufficient to distinguish it from other materials". University of California v. Eli Lilly and Col, 43 USPQ 2d 1398, 1405( 1997), quoting Fiers V. Revel, 25 USPQ 2d 1601m 16106 (Fed. Cir. 1993). See also University of Rochester v. G.D. Searle & Co., 68 USPQ2d 1424 (DC WNY 2003).

***Claim Rejections - 35 USC § 112, second paragraph***

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

In view of the cancellation of claims 1-15, the rejection under 35 U.S.C. 112, second paragraph is moot.

Claims 52-74, newly submitted, are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A. Claim 52 is unclear as to the "individual identifier sequence amino acid tracts which are unique", especially in the absence of positive recitation in the specification. It is not clear as to the meaning of tracts or unique in the context of the claimed amino acid. It is further unclear whether such unique characteristic is exhibited only when bound to the specific target of interest. When applicant acts as his or her own lexicographer to specifically define a term of a claim contrary to its ordinary meaning, the written description must clearly redefine the claim term and set forth the uncommon definition so as to put one reasonably skilled in the art on notice that the applicant intended to so redefine that claim term. *Process Control Corp. v. HydReclaim Corp.*, 190 F.3d 1350, 1357, 52 USPQ2d 1029, 1033 (Fed. Cir. 1999). The terms "specific" and "more" are relative terms which renders the claim indefinite. These terms are not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. It is not

> A person shall be entitled to a patent unless -
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical Amendments Act of 2002 do not apply when the reference is a U.S. patent resulting directly or indirectly from an international application filed before November 29, 2000. Therefore, the prior art date of the reference is determined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

Claims 52-56, 58-70 and 73-74 are rejected under 35 U.S.C. 102(e) as being anticipated by Knappik (USP 6300064).

Knappik discloses e.g., abstract, a library of antibody (protein, as claimed) with synthetic consensus sequences (individual amino acid sequence tracts) having protease cleavage sites. Knappik discloses at col. 7, line 60 up to col. 13, line 3 that the complete collection of (poly)peptide sequences represent the complete structural repertoire of the collection of homologous proteins. These artificial (poly)peptide sequences are then analyzed, if possible, according to their structural properties to identify unfavorable interactions between amino

clear as to the protein is specific to a target of interest, especially since the neither the library or protein sequence is given. Also, there is no maximum limit of the **more** than one protein in the disclosure. It is suggested that "at least " be used.

B. Claim 55 is unclear as to the phrase "two adjacent identifier sequence tracts" especially in a protein that forms a tertiary conformation.

C. Claim 65 is unclear as to the "introduced protease sensitive sites" i.e., as to how said sensitive sites is introduced to the protein sequences. This claim is at odds with the base claim, which recites said protease sites as part of the protein. This rejection has similar import to claim 74. The preamble in claims 64 and 74 recite for identifying but the body of the claim does not recite the identifying steps.

D. Claim 71 is unclear as to the "the released identifier sequence tract(s)" and lacks antecedent support from the base claim. The base claim does not recite for the release of the identifier sequence tracts.

***Claim Rejections - 35 USC § 102***

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

acids within said (poly)peptide sequences or between said or other (poly)peptide sequences, for example, in multimeric proteins. Such interactions are then removed by changing the consensus sequence accordingly. The (poly)peptide sequences are then analyzed to identify sub-elements such as domains, loops, helices or CDRs. The amino acid sequence is backtranslated into a corresponding coding nucleic acid sequence which is adapted to the codon usage of the host planned for expressing said nucleic acid sequences. A set of cleavage sites is set up in a way that each of the sub-sequences encoding the sub-elements identified as described above, is flanked by two sites which do not occur a second time within the nucleic acid sequence. This can be achieved by either identifying a cleavage site already flanking a sub-sequence of by changing one or more nucleotides to create the cleavage site, and by removing that site from the remaining part of the gene. The cleavage sites should be common to all corresponding sub-elements or sub-sequences, thus creating a fully modular arrangement of the sub-sequences in the nucleic acid sequence and of the sub-elements in the corresponding (poly)peptide. Knappik further discloses sets up two or more sets of (poly)peptides (i.e., library), where the cleavage sites are not only unique within each set but also between any two sets. The libraries comprises for example, but not limited to, two

domains from antibodies such as VH or VL or two extracellular loops of transmembrane receptors. Moreover, Knappik discloses libraries of antibodies or antibody fragments, preferably single-chain Fv, or Fab fragments, which may be used as sources of specificities against new target antigens. A method for identifying one or more genes encoding one or more antibody fragments which binds to a target, comprising the steps of expressing the antibody fragments, and then screening them to isolate one or more antibody fragments which bind to a given target molecule is also disclosed. An scFv fragment library comprising the combination of HuCAL VH3 and HuCAL V.kappa.2 consensus genes and at least a random sub-sequence encoding the heavy chain CDR3 sub-element is screened for binding antibodies. If necessary, the modular design of the genes can then be used to excise from the genes encoding the antibody fragments one or more genetic sub-sequences encoding structural sub-elements, and replacing them by one or more second sub-sequences encoding structural sub-elements. The expression and screening steps can then be repeated until an antibody having the desired affinity is generated. Knappik also discloses a method in which one or more of the genetic subunits (e.g. the CDRs) are replaced by a random collection of sequences (the library) using the said cleavage sites. Since these cleavage sites are (i) unique in the vector

system and (ii) common to all consensus genes, the same (pre-built) library can be inserted into all artificial antibody genes. The resulting library is then screened against any chosen antigen. Binding antibodies are selected, collected and used as starting material for the next library. One or more of the remaining genetic subunits are randomized as described above. See further the EXAMPLES at col. 15, line 50 up to col. 28, line 60. Accordingly, the specific library of Knappik and method using said library fully meet the broad claimed library of undefined structure or components.

***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 52-70 and 73-74 are rejected under 35 U.S.C. 103(a) as being unpatentable over Knappik in view of either Ring (USP 5,849,877) or Markland et al (WO 92/15679).

Knappik is discussed above. Knappik fails to disclose that the endoprotease is Factor Xa as in claim 57. However, Ring

discloses at col. 34, line 65 up to col. 35, line 25 the proteolytic cleavage of an isolated sFv from its leader sequence fusions to yield free sFvs, which can be renatured to obtain an intact biosynthetic, hybrid antigen-binding site. The cleavage site preferably is immediately adjacent to the sFv polypeptide and includes one amino acid or a sequence of amino acids exclusive of any one amino acid or amino acid sequence found in the amino acid structure of the single polypeptide chain. The cleavage site preferably is designed for specific cleavage by a selected agent. Endopeptidases are preferred. Many useful cleavage agents, for instance, blood coagulation Factor Xa and enterokinase recognize and preferentially or exclusively cleave at particular cleavage sites. Useful enzymes recognize multiple residues as a cleavage site, e.g., factor Xa (which recognizes a four amino acid sequence of Ile, Glu, Gly and Arg residues, respectively), or enterokinase (which recognizes a five amino acid sequence having four Asp residues, and one Lys residue, respectively). Markland discloses at page 21, lines 5-20 that display peptides having high affinity for the target may be quite difficult to elute from the target, particularly a multivalent target. One can introduce a cleavage site for a specific protease, such as Factor Xa, into the fusion protein so that the binding domain can be cleaved from the genetic package.

Such cleavage has the advantage that all resulting phage have identical coat proteins and therefore are equally infective. The step allows recovery of valuable gene which might otherwise be lost. Accordingly, it would have been obvious to one having ordinary skill in the art at the time the invention was made to use protease digestion in the library of Knappik, specifically Factor Xa for the advantage provided by e.g., Markland above. Such advantage would motivate one having skill in the art since this advantage provides for the recovery of valuable genes which might otherwise be lost if protease cleavage is not used.

Claims 71 and 72 are rejected under 35 U.S.C. 103(a) as being unpatentable over Knappik in view of Markland or Ring as applied to claims 52-70 and 73-74 above, and further in view of Hutchens (USP 6734022).

Knappik is discussed above. Knappik does not disclose mass spectrometry i.e., MALDI-Tof determination of the peptide sequence. Hutchens discloses at col. 5, line 35 up to col. 6, line 60 a method for desorption and ionization of analytes in which unused portion of the analytes contained on the presenting surface remain chemically accessible, so that a series of chemical and/or enzymatic or other treatments (e.g., discovery of analyte-associated molecules by molecular recognition) of the analyte may be conducted on the probe tip or other presenting

surface, in situ, followed by sequential analyses of the modified analyte by mass spectrometry. In one case (i.e., repetitive sequential analyses) the analyte is adsorbed to the sample presenting surface and can be treated (modified in situ after the excess free matrix is removed (i.e., washed away). Matrix can be added back before analysis by mass spectrometry. Using this procedure, an analyte can be repeatedly tested for a variety of components by removing one matrix, modifying the analyte sample, re-applying the same or different matrix, analyzing the sample, etc. or groups of biological or other macromolecules under investigation, or subsequent examination (e.g., quantification and/or structure elucidation) by mass spectrometry. This has the advantage of achieving both the purification of the analyte sample previously required and the effect of concentrating the analyte. It reduces by a factor of 1,000 to 100,000 the amount of analyte needed for the mass spectrometry examination, since only the macromolecules which attach to the biospecific affinity reagents are removed from the analyte sample, and these can be sequestered on predetermined areas of the probe tips or sample plates that are even less than the laser spot size.

It would have been obvious to one having ordinary skill in the art to use MALDI-Tof in the method of Knappik for the

advantage taught by Hutchens. The advantage, supra, would motivate one having ordinary skill in the art.

No claim is allowed.

***Conclusion***

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

This application contains claims 16-51 drawn to a nonelected invention. A complete reply to the final rejection

must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to T. D. Wessendorf whose telephone number is(571) 272-0812. The examiner can normally be reached on Flexitime.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang can be reached on (571) 272-0811. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

T. D. Wessendorf
Primary Examiner

Art Unit 1639

tdw
August 20, 2004